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Review article

Allelopathy and allelochemicals from microalgae: An innovative source for bio-herbicidal compounds and biocontrol research

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ABSTRACT

The intensive use of synthetic herbicides over the past 50 years has led to a number of deleterous impacts on the terrestrial and aquatic environment and is a serious challenge to the ability to sustain agricultural production into the future. In order to remedy this problem, the use of biocontrols is rapidly accelerating and initiating the transition of the agricultural system into an agroecological system. Microalgae (in its wider sense, eukaryote and cyanobacteria) from marine and freshwater habitats are known to produce a diverse range of toxic or otherwise bioactive allelochemical metabolites for growth, communication and defense. Between the search for innovative active molecules and the development of new production processes at the dawn of biotechnology, microalgae have an immense potential in their contribution to biocontrol products. Microalgal organisms can be grown in mass cultures enabelling their manipulation for optimal production of bioactive substances, giving them a significant advantage over terrestrial plants in exploring their effectiveness. In this review we will present the structural diversity of allelochemical compounds and their role for microalgae, the competitive advantages that these compounds provide to microalgae compared to competing species, as well as their potential as biological control agents and bioherbicides.

1. Introduction

The development of agriculture has been accompanied by the need to protect crops through various methods, including biocontrol. Over the past 50 years, many problems related to the extensive use of chemicals (such as environmental pollution and the impact on human health) have emerged. In particular, concerns have included documented toxic effects on human, animal and ecosystem health, as well as an associated potential for bioaccumulation [1–3]. Additionally there is growing evidence of acquired resistance (and cross-resistance) by target species with consequent implications for both cost and sustainability [4,5]. This has lead to the development of various methods of alternative control, including biological control, in order to reduce the use of synthetic biocides. Glyphosate, a synthetic biocide, is the active molecule in one of the world's best-known herbicides: Monsanto's Roundup® (approved in 1974). The patent for this substance fell into the public domain in 2000 and since then, glyphosate has become the most widely used weed killer in the world. In March 2015, the International Agency for Research on Cancer (IARC), an agency within the World Health Organization (WHO), evaluated glyphosate and classified it as a high-impact product on biodiversity. As a result, many actions have been implemented to develop and promote biocontrol strategies, such as support for research and innovation in the field of weed control, support for farmers in the ecological transition, support for the glyphosate phase-out policy in agriculture [6–8]. Biocontrol is an integral part of integrated crop protection strategies, and thus contributes to the development of sustainable but also organic agriculture. The principle of biocontrol rests on managing the balances of pest populations rather than on their eradication. Biocontrol products focus on the use of natural mechanisms and interactions, which regulate the relationships between natural species in their environment. In this context, the search for alternative solutions has turned to molecules and natural products, and a number of articles have been published on the subject of bioactive natural products as a source of potential herbicides [9–11]. On a global scale, only a dozen commercial bio-herbicide-type products based on micro-organisms or natural molecules are currently on the market [12]. Since 2015,

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following the registration in Europe of a new herbicide (Beloukha®) distributed throughout the continent, only thirteen bio-herbicides have been registered, nine are based on fungal microorganisms, three are based on bacterial microorganisms and one contains a natural plant extract as active ingredient [13]. The research and marketing of bio-herbicides is therefore a very under-exploited area. Among the natural resources that can be exploited, aquatic photosynthetic microorganisms (marine or terrestrial), are a potential alternative to be considered for the production of biomass and metabolites of interest.

The marine environment constitutes two thirds of our planet and encompasses a considerable part of its biodiversity. The extensive resources provided form the basis of many economic activities, and for the foreseeable future, the marine environment offers a wide range of biotechnology applications. According to the Green Paper: "Towards a Future Maritime Policy for the Union and the indications set forth by the EU-US Task Force on Biotechnology Research" (Commission of the European Communities, 2006), "blue biotechnology" has an expected growth of 10% per year and an expected world market of 2400 million euros. To date, microalgae remain largely unexplored and represent a unique opportunity to discover novel metabolites and produce metabolites at a lower cost. As a group, the microalgae in its wider sense (including cyanobacteria), are known to produce a remarkable diversity of biologically active metabolites [14–16]. Despite nearly 18,500 new compounds isolated from marine sources between 1965 and 2006, it is estimated that about 97% of all existing marine compounds have not yet been isolated, and have therefore not undergone any chemical or biological characterization [17–19]. In addition to this recognized chemical diversity, a growing body of knowledge supports the notion that many of these bioactive metabolites from microalgae may have specifically evolved in the capacity of allelopathy. Microalgae use allelochemicals to gain competitive advantage via interspecific effects on survival, reproduction and in particular the inhibition of the growth of competing photoautotrophic species. In addition, recent developments in the mass culture of microalgae offer a competitive advantage over other biological agents. Microalgal cultures are highly exploitable and increasingly controlled; they are produced efficiently and sustainably in large open reactors minimizing energy consumption and resource absorption. Operating in full recirculation mode allows for emission-free processes. The technologies developed for harvesting and processing microalga have proved to be effective on a large scale allowing, under stable conditions, for maximum yield cultures. This makes it possible to obtain a continuous annual resource more quickly and at a lower cost than terrestrial plants [20]. The selectiveness of the biocidal effect of cyanobacteria and microalgae and the high technological level of their controlled culture allow for the creation of a new series of preparations for plant protection and pest control [21,22].

Due to the congruency of technological advances in the production of microalgal resources, biological activities of allelochemicals and agrochemical needs, studies on the potential of microalgae metabolites as herbicides have emerged. The objective of this review is to present the roles and diversity of allelochemical compounds produced by microalgae (eukaryote) and cyanobacteria (prokaryote) in both fresh water and marine environments, the competitive advantages that these compounds provide to microalgae and cyanobacteria compared to competing species, as well as their potential as bio-herbicide and biological control agents.

2. Defining allelopathy

Allelopathy is a biological phenomenon in which an organism produces one or more biomolecules that affect the growth, survival and/or reproduction of other organisms. The term allelopathy was introduced by Molisch [23] in 1937, while studying the phenomenon of one plant influencing another (from the Greek "allelos", mutual, and "pathos", suffering). However allelopathy has been observed since antiquity (~3000 BCE) where Greek botanist Theophrasus first observed the effect of chickpea plants on depleting soils and destroying the surrounding weeds [24]. The concept of allelopathy, initially negative, was redefined, as the "product of direct or indirect effects (harmful or beneficial) of one plant (or microbes) on another plant by releasing compounds into the environment" [25,26]. The International Allelopathy Society (IAS), defines allelopathy as the science that "studies any process involving secondary metabolites produced by plants, algae, bacteria and fungi that influence the growth and development of agricultural and biological systems" [27]. This definition was then expanded and used in the literature to describe the chemical interactions between different organisms and chemical communication in general [24].

The biomolecules involved in allelochemical processes can be secondary metabolites (not directly involved in fundamental physiological processes of an organism) or primary metabolites (involved in the normal growth, development and reproduction of an organism or cell). They are called allelochemicals. They may have a beneficial effect (positive allelopathy) or a negative effect (negative allelopathy) on the target organism and surrounding organisms. Inderjit and Keating [28] also suggested using the term "allelochemistry", since allelopathy evokes only negative effects (see above the meaning of pathos in Greek: to suffer). Macías and Galindo [29] have proposed that the term "bio-communicator" refers to "every chemical or mixture of chemicals used by living organisms to exchange information." The use of the two terms, "allelochemical" and "bio-communicator" covers a range of chemicals used by organisms to exchange information, from pheromones and allomones to poisons, toxins, deterrents, phytoalexins. These chemicals govern most of the behaviors of organisms, from defense attack responses to warning signals or social conduct. Another term, sometimes misused, is "regulatory plant growth," which is "any chemical, natural or synthetic, that can influence plant growth and development." An allelopathic agent could be considered as a growth regulator, the main difference being that an allelopathic agent must be introduced into the environment to fulfil its protective role [30].

One of the most contentious points is to distinguish between allelopathy and competition [31] because some authors maintain that allelopathy is part of the competition for resources (light, nutrients, carbon dioxide). However, it is impossible to separate the two mechanisms in natural systems [32]. The joint analysis of all factors that could affect the allelopathic process could also show a synergistic, additive or even antagonistic effect, encompassing the allelopathic relationship in a more complex environment than a simple laboratory experiment.

In this article, we will use the term allelopathy in the context of the negative/positive effect of allelochemicals produced by microalgae on other groups/species and between microalgae too.

3. Allelopathy in fresh water and marine environments

The concept of allelopathy is generally accepted by scientists as an eco-physiological process but, since the phenomena are very difficult to demonstrate in the field, their importance in aquatic systems is still debated. Methodological difficulties in studying chemical interactions between species in fresh water and marine ecosystems, including consideration in modeling hydrodynamic, chemical and biological factors at different time and space scales, are the reason why this eco-physiological factor has been underestimated in marine plant competition. Allelopathy is a dynamic process that is extremely complex. The analysis of chemical and biological variables involving both simple effects and the dependent effects of multi-scale factors is very difficult, which means that detailed investigations are always necessary [33]. In this sense, little is known about the role of allelopathy in the marine environment [34]. Despite the potential importance of allelopathic processes in the marine environment, due to the difficulties mentioned above, very few ecological models include allelochemistry [35]. However, it is clear that such an important process should be included in future models that take into account interactions between species [36].

While some researchers consider allelopathic interactions to be

closely associated with competition for resources [37], others equate them with a defense mechanism [38]. In general, algal allelopathy could operate in four ways: the chemicals of one algae affecting the growth of another alga, chemicals secreted by algae inhibiting their own growth (i.e., algae self-toxicity), algal toxins influencing the growth of other microorganisms, and algal toxins affecting the growth of higher plants [39].

Microalgal allelopathy can have a negative impact on predator performance, resulting in death or growth inhibition. This chemical defense strategy has been widely demonstrated in toxic algae during bloom formation [40]. The frequency and diversity of toxins released by microalga suggests that allelochemical production may play a fundamental role in competition between algal species. The most promising studies are on already proven complex mechanisms such as those in which microalgae feed on predators known as phagotrophy (ingestion of large food particulate) [41,42]. Some studies have shown higher growth rates of microalgae when using phagotrophy mechanisms. Among them, the *Chrysochromulina* and *Prymnesium* species have vitamin B1 and B12 requirements that they draw from their environment by phagotrophy [43]; as an example *P. parvum* and several *Chrysochromulina* species can ingest particles such as bacteria and microalgae and are therefore mixotrophic [43]. Many dinoflagellates such as *Gonyaulax polygramma* [44], *Alexandrium tamarense* [44], *Ceratium furca* [45], *Dinophysis acuminate* [42] are able to perform phagotrophy. The prey can be immobilized or killed by toxin(s) before ingestion [46,47]. So far, it has not been shown that phagotrophy is triggered by an allelopathic phenomenon.

In contrast, allelopathy can also be considered as a source of stability in the environment; for example, phytoplankton allelopathy at sea promotes a stable coexistence of competitive phytoplankton species that would otherwise lead to the competitive exclusion of weaker species [48]. Secondary metabolites in phytoplankton are assumed to regulate and control the biology of phytoplankton, the succession of phytoplankton species, competition and intra- and interspecies communication [49]. Allelopathic interactions are therefore an important factor in determining the distribution and abundance of species within plant and planktonic communities [40]. As a result, allelopathy is an adaptation by which some phytoplankton species may gain a competitive advantage over other species [49].

Proximity between donor and target species is the first condition for allelopathic processes to occur. Emitting species can affect target species in many ways. In most instances, they release allelochemicals into the environment, which come into contact with the cell membranes of the target species [37]. However, there is another less common process in aquatic environments: cellular contact [50]. The modes of action are still poorly understood but may include damage to cell membranes, inhibition of protein activity or modification of physiological function [49].

In most cases, allelochemicals kill target species, causing a decrease in their biomass. However, if allelopathic substances are present in the environment or are released in low concentrations, the defense responses of target species (in order to stabilize a minimum biomass sufficient to persist in the environment) can be sexual induction or encystment [38]. Thus the sensitivity of the target species of allelopathic substances depends on the concentration of the microalgal receptor, the species or the target group of microalgae or algae [37]. The ecophysiological state of the target organism also plays a role in its sensitivity and its ability to respond to substances. The physiological state and inherent characteristics of target species strongly determine their degree of resistance or detoxification to allelochemicals [51]. Target organisms can suffer sub lethal damage that allows them to continue living because they maintain a positive growth rate. However, the growth rate is lower than the rate produced in the absence of emitting or receiving species [52]. The process of osmotrophy (ingestion of dissolved organic compounds) can accompany the allelopathy caused by microalgae. After being lysed, zooplankton predators of microalga can serve as a source of nutrients for microalgae. Hattenrath-Lehmann et al. [53] showed that by killing co-occurring phytoplankton species as well as bacteria, allelopathic species can use not only nitrogen and inorganic phosphate of limited availability in the surrounding waters, but also organic nitrogen and phosphate released by lysed target cells. Rengefors et al. [54] showed higher growth rates in microalgae when using osmotrophy mechanisms. Osmotrophy mechanisms indicate that the target undergoing sub-lethal damage can be used to maintain a positive growth rate.

4. Biotic and abiotic factors affecting the production and accumulation of allelochemicals

Abiotic factors represent all the physico-chemical factors of an ecosystem that have an influence on a given biocenosis. It is the action of the non-living on the living. Conversely, biotic factors are related to the activity of living beings and act on the distribution of animal and plant species in a given biotope. Many abiotic and biotic factors influence toxicity and affect the production of allelopathic substances produced by algae [37].

4.1. Abiotic factors

Of all the abiotic factors that promote allelopathy, the most important are: nutrient deficiency (nitrogen and phosphorus), low temperatures and a high pH culture (~pH 9.0). Positive stimulation increases the secretion of allelochemicals from emitting species and is associated with competition for resources [37,38]. After the development of a bloom under eutrophic conditions, certain microalgae responsible for the formation of bloom continue their development under limiting conditions due to their ability to capture and use carbon dioxide (CO_2) [55,56], their ability to use bicarbonate ion (HCO_3^-) even with high pH conditions, as well as the ability to fix and use N_2 [57]. Hattenrath-Lehmann et al. [53] have shown that when allelopathic species experience limiting and/or unbalanced conditions in N and P, the production of allelochemicals is stimulated.

Conversely, the most important abiotic factors that act as allelopathy repressors are: high light intensities, high temperature, excessive nutrients in the culture medium (nitrogen and phosphorus), and crops with low pH values (~pH 6.0) [37]. The chemical structure of toxic compounds and the mechanisms by which abiotic factors stimulate or inhibit allelopathy appear to not be totally elucidated [58]. As an example, Roelke et al. [59] studied the effect of nutrient enrichment on microalgae *Prymnesium parvum* and its toxicity during bloom formation. During the experiment, a bloom of *P. parvum* occurred, coinciding with a high fish mortality as well as a golden coloration of the water with foam on the surface. In treatments that received nutrient addition (N, P) they observed reduced fish toxicity and reduced sublethal effects on zooplankton reproduction *Daphnia magna* [59]. Addition of N and P increased the density of *P. parvum* but also favoured the increase of other groups of algae, which competed with the toxic microalgae and reduced its harmful impact. If the allelopathic organism and the target have different nutritional preferences and are therefore in different states of nutrient limitation, the effects may be less pronounced. This means that there will be a reduced amount of allelochemicals produced and/or the target will be more resistant. Schmidt and Hansen's [60] work on the allelopathic effects of *Chrysochromulina polylepis* (haptophyte) on the dinoflagellate *Heterocapsa triquetra* showed the toxicity of low cell density cultures increased at pH 8–9, while toxicity disappeared at pH 6.5–7. High pH had a first negative effect on the motility of *H. triquetra*. Moreover, the presence of *C. polylepis* allelochemicals in the medium exacerbated the motility problems of *H. triquetra* [60]. Similar results were also found for the freshwater cyanobacteria *Oscillatoria laetevirens* [61].

4.2. Biotic factors

An important biotic factor to consider is the growth phase of allelopathic species: it has been shown that the intensity of the allelopathic

effect depends on the growth phase. Schmidt and Hansen [60] and Suikkanen et al. [62] have shown that the allelopathic effect is caused by cells that increase exponentially, that these effects decrease in the stationary phase, and that senescent cells do not cause allelopathic effects. Some species (e.g., *C. polylepis*) can lose their toxicity after a few days of stationary growth [60]. As allelopathy is a form of competition, it is logical that allelopathic species are more virulent during exponential growth, while the cells may benefit from their effects.

Another important biotic factor to take into account is the cellular concentration of microalgae, which is decisive in the production of the toxin specific to the target cell. Studies have shown that a high concentration of the microalga *Heterocapsa circularisquama* in the presence of ciliates can lead to their death due to an effect similar to "quorum sensing" (QS) (a cell-density dependent system for information transfer between microorganisms) [63–65]. Specifically, Chi and colleagues [63] have shown that quorum sensing systems for bacteria associated with microalgae can regulate algicidal activity. The researchers isolated from the microalga *Prorocentrum donghaiense* a marine bacterium, *Ponticoccus* sp., which is regulated by quorum sensing via N-acyl-homoserine lactone (AHL). The bacterium also showed algicidal activity against its host *P. donghaiense*. The addition of β-cyclodextrin to the culture medium, which binds to AHL and inhibits the QS system, reduced algicidal activity by more than 50% without inhibiting bacterial growth. This indicates that QS inhibition may affect the production of algicidal metabolites of *Ponticoccus* sp. strain. Similarly, the dinoflagellate *Peridinium gatunense* and the cyanobacterium *Microcystis* sp. showed growth inhibition as a result of effects associated with allelopathy [66]. However, the effect of cell concentration can be modulated by pH or growth phase: Schmidt and Hansen [60] found a quantitative change in the pH toxicity response for three different cell concentrations of toxic algae. For example, a very dense and highly toxic *C. polylepis* culture was toxic at pH 8 or 9 but not at pH 7; similarly, a *C. polylepis* culture lost its toxicity even though the cell density was very high after a few days of stationary growth.

Biotic factors such as high density, stage of growth and, in summary, the overall ecophysiological state of microalgae, could alter the allelopathic activity of emitting species [37]. A study of the effect of these factors therefore represents an indispensable step for the recovery of microalgae in order to optimize biomass production yields and of the compound(s) of interest.

5. Allelochemicals in microalgae

Aquatic systems have a greater diversity of species and chemical compounds than in terrestrial ecosystems [67]. As an example, microalgae produce a remarkable diversity of biologically active metabolites. Among them, allelochemicals have received special attention in recent years. It became apparent that allopathy was an important factor in explaining community structure, population dynamics and the chemical defense of microalgae against predators and potential grazers (including larvae of aquatic invertebrates). Bioactive metabolites from microalgae offer a competitive advantage thanks to interspecific and particularly negative (i.e., inhibitory) effects on the growth, survival and reproduction of antagonistic species. In conclusion, they are a source of new antimicrobial agents and bio-herbicides [22,30,68].

Initially, toxins were considered to be allopathic compounds that inhibit the growth of competing microalgae, as in the case of domoic acid or okadaic acid (Fig. 1) [69,70]. However, several studies have shown that this hypothesis is not certain [71,72]. In most of the studies in which an allelopathic effect was described, the effect of pH was not taken into account although it plays a key role in the growth of microalgae [73]. The inhibition of growth may be due to an increase in pH in the environment rather than to the release of toxins by the microalgae. Experiments with the addition of domoic acid in different phytoplankton cultures showed that the growth rates of phytoplankton were identical, whereas phytoplankton growth declined when pH values >9 were

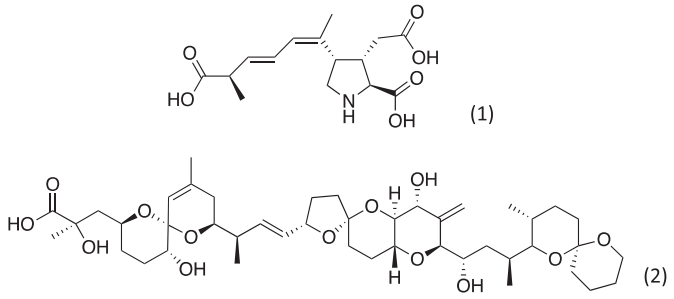

Fig. 1. Domoic acid (1) and okadaic acid (2).

reached after a few days of cultivation [71]. In this case, the results obtained may potentially be false positives and a cautious interpretation is warranted. Because of these types of methodological errors, the allelopathic capacity of some species or strains has recently been questioned [74,75].

The secondary metabolites of microalgae include all the chemical classes of natural products, ranging from fatty acids to alkaloids, including numerous peptides and amino acids. More than 550 secondary cyanobacterial metabolites have been discovered, mainly peptides derived from non-ribosomal synthesis (NRPs) but also a significant number of alkaloids and polyketide derivatives, which are often complex and bioactive [76,77]. However, knowledge about the chemical identity of metabolites involved in allelopathic interactions and their biosynthetic pathways [38] as well as the quantitative aspect of interactions remains scant. Despite this lack of information, Gross [78] explained that allelopathic relationships between submerged macrophytes, benthic algae and cyanobacteria are frequently observed even if the mechanisms are not known.

5.1. Free fatty acids

Several allelochemical compounds synthesized by the green microalgae *Botryococcus braunii* have been described and favour its dominance in its natural environment [80]. These compounds are a mixture of free fatty acids, including palmitic, oleic, linoleic and α-linolenic fatty acids (Fig. 2). Fatty acids become toxic to phytoplankton only when they are released by the microalgae in the extracellular medium. A hypothesis has been proposed by the authors [80] to explain the high toxicity of these fatty acids under environmental conditions. In habitats with pH between 8 and 9, free fatty acids exist in an ionised form, namely $RCOO^-$, a form described by Procter et al. [80] as more toxic to aquatic organisms than protonated forms (or neutral) and, by Venediktov et al. [79], as having a more effective inhibitory action on electron transport in chloroplast than the neutral form of fatty acids [79,80]. These statements must nevertheless be modulated by the fact that fatty acids enter the cells in the RCOOH form (before acting on photosynthesis) and are as such more toxic, and that the toxicity of the ionised forms is

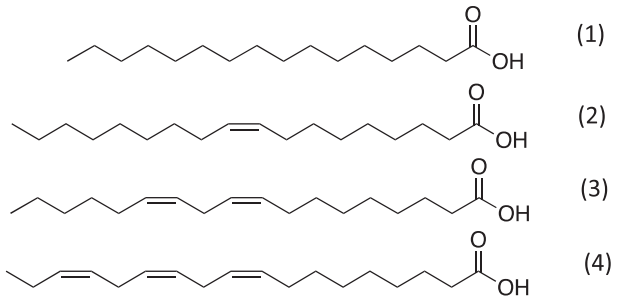

Fig. 2. Palmitic acid (1), oleic acid (2), linoleic acid (3) and α-linolenic acid (4).

reduced by their association with salts under environmental conditions [81].

A number of fatty acids may have inhibitory, stimulating or anti-fouling effects, and are believed to be allelopathic chemicals. Chlorellin, which is a product of the photo-oxidation of unsaturated fatty acids, inhibits the growth of *Chlorella pyrenoidosa* [82]. Chlorellin consists of a mixture of C18 fatty acids (mainly stearic, oleic, linoleic and linolenic acids), and its effects were observed during the co-culture of *C. vulgaris* and *Pseudokirchneriella subcapitata*. At low chlorellin concentrations, the authors observed growth stimulation for both algae. However, at higher concentrations, inhibitory effects on both species were observed [83]. The authors suggest that the high prevalence of linoleic and linolenic acids in this fatty acid mixture could contribute to the observed allelopathic effect.

Another free fatty acid produced by *Lyngbya aestuarii*, 2,5-dimethyldodecanoic acid (Fig. 3), is described by Entzeroth [85] as a compound with strong herbicidal activity. The authors show that at lower pH values the acid is less ionised and enter the cell membrane more readily, resulting in greater toxicity.

Other effects, such as antimicrobial activity, membrane disturbance and product oxidation, inhibition of secondary messengers used in biochemical pathways, and inhibition of phospholipases have been reported for algal polyunsaturated fatty acids.[74,75].

5.2. Alkaloids

A number of metabolites associated with allelopathy and belonging to the indole class of alkaloids have anti-algal activity. The most commonly cited allelochemicals for cyanobacteria are hapalindoles and its derivatives such as 12-*epi*-hapalindole, ambiguines, welwitindolinones and fischerindoles whose structures include an isonitrile type function (Fig. 4).

These last three were isolated from freshwater and seawater cyanobacteria of the Hapalosiphonaceae family and, in particular, from the genera *Hapalosiphon* and *Fischerella* [76,86,87]. From the Calothricaceae family, the cyanobacterium *Calothrix* sp. synthesizes an alkaloid with an indolophenanthridine moiety, calothrixine-A (Fig. 5), capable of killing different types of organisms such as bacteria and fungi. This allelopathic compound inhibits RNA synthesis and DNA replication of *Bacillus subtilis*, which has the effect of inhibiting protein synthesis [88].

Fischerellin A (Fig. 6), produced by *Fischerella* sp., is an alkaloid that specifically inhibits photosystem II (PSII) while contributing to thylakoid degeneration [89]. The mechanisms of action are described in Section 6.3.1. Norharmane (Fig. 6), isolated from cyanobacteria of the genus *Nostoc* and several other genera [90], is an alkaloid responsible for the inhibition of an enzyme equivalent to indoleamine 2,3-dioxygenase which is involved in tryptophan catabolism.

Some cyanobacterial indole alkaloids are structurally identical to plant hormones like cytokinins and auxins. Among the phytohormones, the indole-3-acetic acid (Fig. 7) is synthesized by the genera *Nostoc*, *Chorogloeopsis*, *Calothrix*, *Plectonema*, *Anabaena*, etc. [91]. The first time that molecules from microalgae were discovered as plant growth regulator was in 1979 [92]. Since then, Jäger et al. [93] showed that cyanobacterial metabolites like 2,4-dichlorophenoxyacetic acid can replace auxin during plant cells growth.

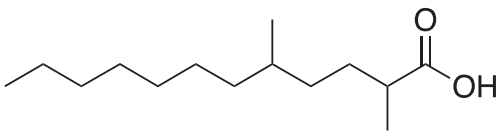

Fig. 3. 2,5-dimethyldodecanoic acid.

5.3. Lactones

Cyanobacterin (Fig. 8) is a chlorinated γ-lactone, isolated from the genus *Scytonema*, a photosynthetic cyanobacteria [94–96]. This cyanobacterium specifically inhibits a wide range of microalgae, including cyanobacteria and green algae, with concentrations on the order of micromolar of cyanobacterin [97]. Its mode of action is mainly based on the inhibition of photosystem II [68,98,99].

Another important lactone, N-acyl-homoserine lactone (AHL) (Fig. 8), is a signalling molecule produced by the bacteria of the microalgal-bacteria consortium [63,100]. These signalling molecules produced inside the cell and released into the environment make it possible to coordinate the behaviour of bacterial groups as a function of AHL concentration and therefore population density. Bacterial AHLs are involved in communication with microalgal cells and stimulate self-aggregation of *Chlorophyta* sp. by producing bio-macromolecules, such as aromatic proteins [100]. Bacterial AHLs affect the growth and enzyme expression of bacteria, and could potentially influence the synthesis of microalgal cells and their production of fatty acids.

5.4. Aldehydes

Polyunsaturated fatty acids (PUFAs) can be decomposed by enzymes through various lipoxygenase pathways to form polyunsaturated aldehydes, hydroxyl acids, halogen metabolites, and all types of oxylipins [101]. The most toxic oxylipins were first discovered in marine and freshwater diatoms. But the decadienal polyunsaturated aldehyde is the most studied polyunsaturated aldehyde (PUA) for its allelopathic effects [101]. The molecule acts on the defense response of diatoms against copepods. In order to reduce their reproductive success and therefore their impact, diatoms will produce PUAs which will limit cell division within copepod embryos and promote apoptosis. PUAs (2*E*,4*E*)-deca-2,4-dienal (Fig. 9), (2*E*,4*E*)-octa-2,4-dienal and (2*E*,4*E*)-hepta-2,4-dienal, have a toxic allelopathic effect on the chlorophyte *Tetraselmis suecica*, the diatom *Skeletonema marinoi* and the dinoflagellate *Amphidinium carterae* [102]. In diatoms, (2*E*,4*E*/*Z*)-deca-2,4-dienal induces a cellular signalling process. Decadienal can induce nitric oxide (NO) production by a calcium-dependent enzyme, resulting in cell death. The antibacterial activity of these compounds has been described by Balestra et al. [103].

5.5. Peptides

Microcystins and nodularins are cyclic peptides containing two atypical amino acids: *N*-methyl-dehydroalanine or Mdha and 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyl-4,6-dienonic acid or Adda (Fig. 10). Microcystins contain 7 amino acids with two variable amino acids on the X and Z positions of the molecule [104]; nodularins have only 5 aminoacids [105]. To date, more than 100 variants of microcystins have been identified and 8 variants of noduralins have been described [106]. Microcystins are produced by cyanobacteria belonging to several genera, *Geitlerinema*, *Synechococcus*, *Nostoc*, etc. [107], while nodularins have been identified only within the genus *Nodularia* [108]. These peptides belong to the group of cyanotoxins and have hepatotoxic activity. They are powerful inhibitors of eukaryote phosphatases of type 1 and 2A [109].

The cyanobacteria *Anabaena flosaquae* produces an exudate composed of alkaloid neurotoxins anatoxin-a and saxitoxin, and microcystins, which considerably reduces the growth of green algae *Chlamydomonas reinhardtii* [110]. In order to defend itself, *C. reinhardtii* produces high concentrations of extracellular products, which form a defensive barrier and thus inhibit the accumulation of microcystins. Studies show that the accumulation of cyanobacterial toxins can be regulated in some species by a complex mechanism dependent on growth phase and environmental conditions [110]. Another cyclic peptide produced by *Chlorella vulgaris*, portoamide (Fig. 11), specifically

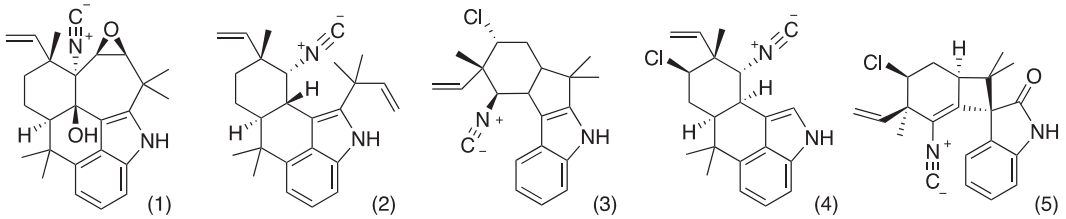

Fig. 4. Ambiguine I (1), ambiguine H (2), fischerindole L (3), hapalindole A (4) and welwitindolinone A (5).

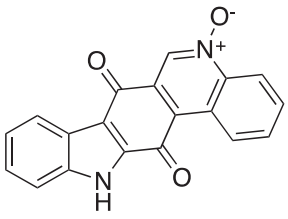

Fig. 5. Calothrixin-A.

inhibits the growth of receptor species. This metabolite has a strong growth inhibitory impact on *Cylindrospermopsis raciborskii* while other cyanobacteria such as *Microcystis* sp., *Aphanizomenon* sp. and *Anabaena* sp. are not inhibited [111]. Other peptides such as cryptophycins, curacins or dolastatins (Fig. 11) are known to inhibit cell division and are presented in chapter six.

Majusculamide C (Fig. 12), a cyclic depsipeptide from *Lyngbya majuscula*, was described by Moore and coworkers in 1982 [112] and is subject of a patent application for its anti-fungal activities. Finally, nostocyclamide (Fig. 12), a peptide produced by cyanobacteria of the genus *Nostoc*, inhibits PSII by preventing the transport of electrons [113].

5.6. Extracellular metabolites (exopolysaccharides, extracellular proteins and lipids)

Exopolysaccharides (EPS) belong to a group of high molecular weight biopolymers secreted by microalgae into the environment during their growth [114–116]; they can either be attached to the cell wall or excreted into the environment [117,118]. Many microalgae, particularly red microalgae and cyanobacteria produce a wide variety of EPS and are structurally diversified. The role of EPS in the physiology and interaction of microalgae is not fully understood; however, several

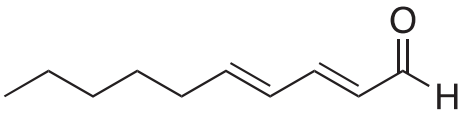

Fig. 9. (*2E*, *4E*)-deca-2,4-dienal.

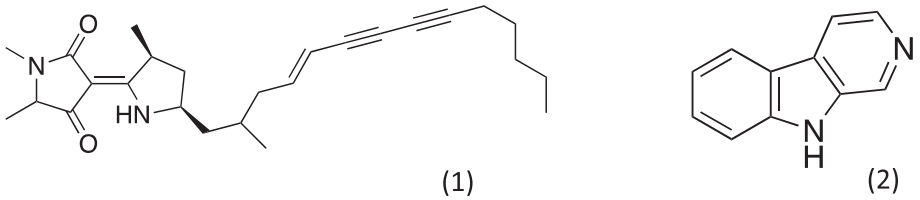

Fig. 6. Fischerellin A (1) and norharmane (2).

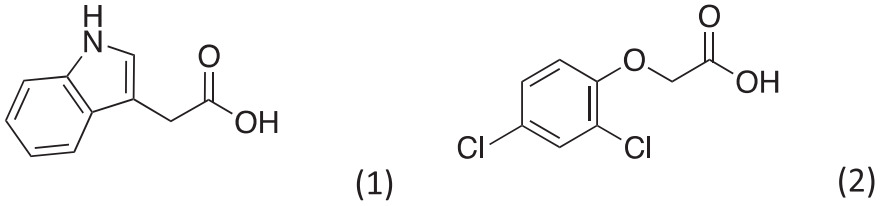

Fig. 7. Indole-3-acetic acid (IAA) (1) and 2,4-dichlorophenoxyacetic acid (2).

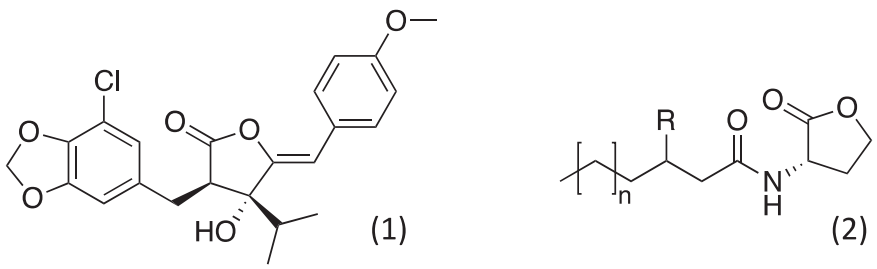

Fig. 8. Cyanobacterin (1) and N-acyl-homoserine lactone (2).

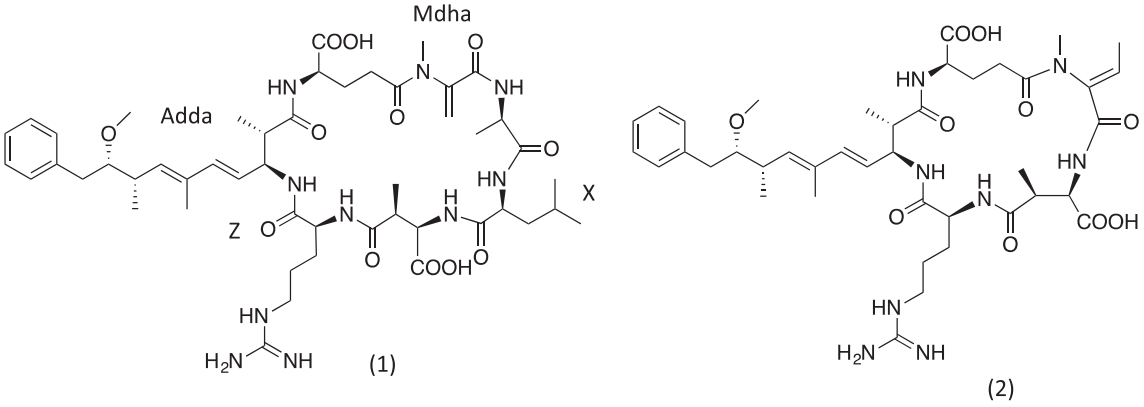

Fig. 10. Microcystin LR with atpycal amino acids (1) and nodularin R (2).

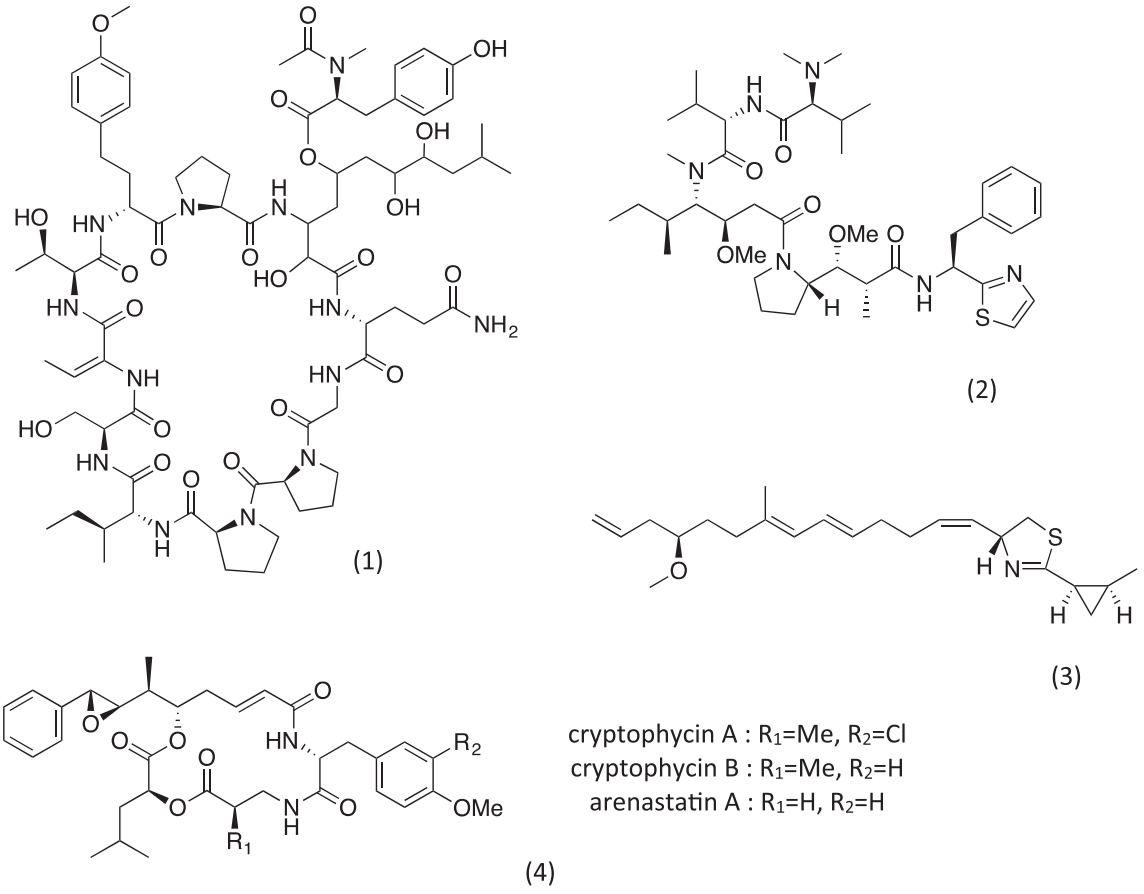

Fig. 11. Portoamide A (1), dolastatin 10 (2), curacin A (3) and cryptophycins (4).

potential functions have been identified. Under stressful conditions, microalgae produce large amounts of EPS for cellular protection. EPS can potentially protect cells from environment related stress [119]. Intra- and extracellular polysaccharides may also be involved in modulating the activity of allelochemicals [120,121]. For example, polysacharide production has been observed in *Anabaena* PCC 7120, *Chlorella vulgaris*, and other microalgae as an adaptive response to microcystins from raw extracts of *Microcystis aeruginosa* [122,123].

Some studies have shown that the activity of extracellular enzymes is of algal origin [124,125]. Microalgal released *exo*-enzymes include alkaline phosphatases, chitinases, glucosidases, proteases and can influence microorganism growth, chemical signalling and biogeochemical cycling in ecosystems [126]. As an example, Karseno et al. [127] showed that the cyanobacteria *Oscillatoria* sp. and *Scytonema* sp. release an extracellular phycoerythrine-like protein. This pigment, from the phycobiliprotein family, inhibits the growth of the green algae *Chlorella fusca* and *Chlamydomonas* sp. and can potentially be used as an algicide.

The extracellular lipophilic substances of microalgae are targeted for the development of unique bioprocesses. For example, *Ochromonas danica* secretes a mixture of free fatty acids (FFA) in its growth medium. This mixture consists of a high proportion of polyunsaturated fatty acids, mainly linoleic, α-linolenic and arachidonic acids. In addition, *Ochromona* grown under mixotrophic conditions have a significantly different extracellular and intracellular production than photoautotrophic culture [128]. In this case, FFA and glycerol-related fatty acids can be used in biodiesel production. In order to minimize production costs and

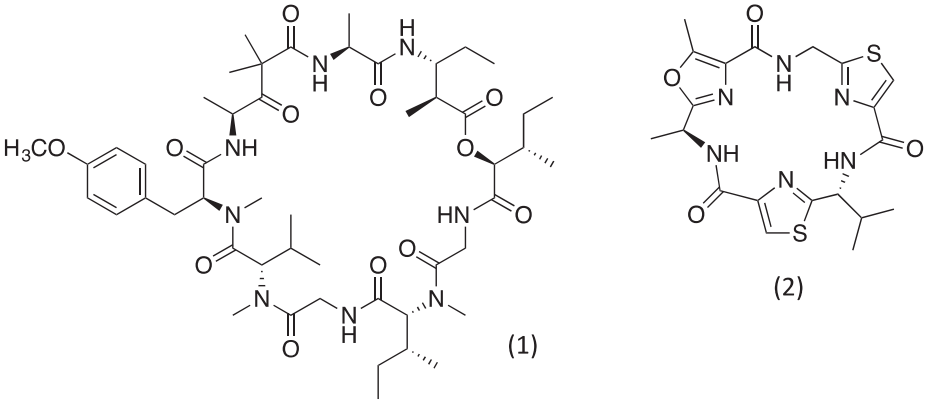

Fig. 12. Majusculamide C (1) and nostocyclamide (2).

maximize yields, a single bioprocess will allow combining all the production steps of the substance in a single process.

6. Microalgae, Bio-herbicidal Technology, Biocontrol and Commercial Potential

Microalgae are among the first living creatures, about 3.5 billion years ago. Their use dates from more than 2000 years in China where people used microalgae belonging to the genus *Nostoc* to survive during periods of famine [129]. Nevertheless, their production is more recent (about 50 years in Europe and 60 years for Japan) and their spectrum of use is extensive. Due to their adaptation to all environments but also because of their more or less abundant production of bioactive metabolites, microalgae offer a wide range of technological choices [130].

However, microalgae have multidisciplinary ways of improvement and enhancement can be valued in a wide variety of fields such as [129,131,132]:

- Agriculture: inputs for organic farming and agro-ecology (fertilizers and sanitary treatments of plants and animals by the supply of minerals and stimulators of natural defenses and phyto-hormones (biomimicry) [133]);
- Human nutrition: direct consumption of algae or extraction of additive components (pigments dyes: carotenoids, blue, red, yellow and green pigments; texturizers; aromas; fats) [134];
- Human and animal phyto-pharmacy (pigments; essential amino acids; molecules of antioxidant interest: catalase, polyphenols, tocopherols; nutrition prophylaxis drugs: unsaturated fatty acids, omega-3 and omega-6 polyunsatured fatty acids; anti-inflammatory and anti-mutagenic agents; compounds involved in restoring resistance to cancer; virtually all vitamins A, B1, B6, B12, C, E; prophylaxis in neurology and ophthalmology) [135,136];
- Animal feed: aquaculture (food for fish and crustaceans, unique food source for hatcheries), source of protein and/or nutritional supplements for livestock and pets [137,138];
- Cosmetics: many products contain ingredients (lipids, vitamins, Mycosporine-like-AminoAcids, pigments, etc. [139]) from microalgae in their formulations [140];
- Energy production: algo-fuels mainly diesel, but also ethanol and biogas (using microalgae as methanization inputs) [141,142];
- Bio-sourced materials: algal bioplastics, construction additives (concrete and bitumen, building materials), adhesives, polysaccharides, polyesters and hydroxy acids [143];
- Bio-remediation: sanitation, and management of industrial and organic waste in urban and rural areas (plant gas and wastewater treatment plant) [144].

Entering the era of sustainable development should enable microalgal exploitation, as they often meet the requirements of the bioeconomy: a circular, decarbonised, decentralised and therefore territorial economy, in participatory networks. However, there are serious uncertainties on the transition time as profound changes are necessary in terms of institutional frameworks (taxation of fossil carbon and organic carbon, regulation of novel foods, etc.) [145].

6.1. Microalgae as potential biocontrol products

Microalgae are used in agriculture as bio-fertilizers, fertilizers, soil stabilizers or crop protectors. Thanks to their ability to fix nitrogen, microalgae and in particular cyanobacteria, maintain soil and crop fertility, thereby increasing the growth and yield of plants and rice as a natural bio-fertilizer [146]. The importance of cyanobacteria in rice cultivation in the agricultural environment is directly related to their ability to fix nitrogen even in the dark. In addition to increasing the level of bio-available nitrogen, their use improves the soil's physical and chemical properties through the long-term gradual accumulation of residual nitrogen and carbon in the soil. Cyanobacteria belonging to the genus *Nostoc*, *Anabaena*, *Tolypothrix* and *Aulosira* fix atmospheric nitrogen and are used as an inoculant for paddy rice crops grown in both high and low altitude conditions. *Anabaena* in association with *Azolla* contributes to an increase in nitrogen levels (up to 60 kg/ha/season) and enriches the soil with organic matter [147]. Moreover, the quality of rice grains in terms of protein content is significantly increased.

In modern agricultural practices, conventional methods of pest control have not been very effective due to the survival of the reproductive structures of pathogens in the soil. At the same time, chemical pesticides inhibit the growth and development of field crops [148].

The antifungal activity of cyanobacteria is widely documented. The studies of Chaudhary et al. [149,150] showed that modified compost with cyanobacteria is more effective in the treatment of diseases caused by phytopathogenic fungi such as *Fusarium oxysporum*, *Pythium debaryanum*, *Pythium aphanidermatum* and *Rhizoctonia solani*. Natarajan et al. [151] and Gupta et al. [152] identified two fungicidal compounds (a benzoic acid derivative (Fig. 13) and a majusculamide C derivative) from the two cyanobacteria, *Calothrix elenkinii* and *Anabaena laxa*, respectively. It was also in 2012 that Gupta et al. [153] identified and characterized antifungal compounds homologous of chitosanase and microcystins (Fig. 10) in the cyanobacteria *Anabaena laxa*, *A. iyengarii* and *A. fertilissima*. The cyanobacterial species *Calothrix elenkinii* produces fungicidal compounds effective against damping-off seedling blight in tomatoes, chilli and eggplant [148]. *Anabaena variabilis RPAN59* and *A. laxa RPAN8* help reduce the growth of *Fusarium jaundice* when inoculated into compost-vermiculite under controlled conditions [150]. In another study, Najdenski et al. [154] identified significant and promising antibacterial and antifungal activities in the cyanobacterial strains of *Synechocystis* and *Gloeocapsa*. The cellular constituents of

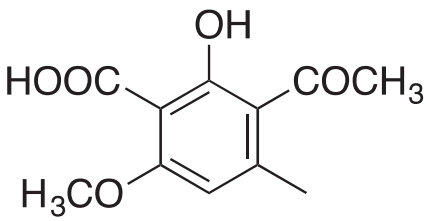

Fig. 13. 3-acetyl-2-hydroxy-6-methoxy-4-methylbenzoic acid.

cyanobacteria tested on work by Kulik [155], reduced the activity of *Botrytis cinerea* on strawberries, decreased the activity of *Erysiphe polygoni* (powdery mildew on turnips and seedling blight on tomatoes), reduced the growth of saprophytes such as *Chaetomium globosum*, *Cunninghamella blakesleeana*, and *Aspergillus oryzae*, and plant pathogens such as *Rhizoctonia solani* and *Sclerotinia sclerotiorum* [155]. Several researchers have reported that compounds similar to fischerellins (Fig. 6) isolated from *Fischerella muscicola*, exhibit antifungal activity against phytopathogenic fungi such as *Uromyces appendiculatus* (brown rust), *Erysiphe graminis* (mildew), *Phytophthora infestans* and *Pyricularia oryzae* (rice stem necrosis) while less effective against *Monilinia fructigena* which causes brown rot and *Pseudocercosporella herpotrichoids* which induces necrosis of the stems [87,156].

Nostoc muscorum has antifungal effects against soil fungi, especially those that produce damping-off [157] but also against *Sclerotinia sclerotiorum*, one of the most common phytopathogens, which causes "white mould", mainly affecting lettuce and other rosette plant species [158], against fungi that cause "blue stain in wood" [bluish or greyish discoloration of sapwood caused by certain dark-coloured fungi (*Aureobasidium*, *Alternaria*, *Cladosporium*, etc.)] on the surface and inside the wood [159], against *Rhizoctonia solani* (root and stem rot [155]). In addition, Biondi et al. [160] have shown that the genus *Nostoc* is also a potential producer of natural pesticides against insects and nematodes.

However, few studies have been conducted to assess the efficacy of microalgae toxins as herbicide on higher plants, while the algicidal activity of allelochemicals from microalgae has been widely explored. Consequently, current knowledge of the herbicidal potential of microalgae is limited. Given the importance of allelopathy in the relationships between photo-autotrophic aquatic organisms, and the presumed biochemical and physiological homologies between algae and higher plants, microalgae are probably an extremely rich source of herbicide-like compounds. As such, two approaches are proposed as a means of exploring the chemical repertoire of these taxa with respect to herbicide biocontrol products:

- An in vivo bio-analysis approach, based on the identification of phytotoxicity against weeds,
- A target-based approach, by specifically designing trials based on known herbicide targets

6.2. Microalgae herbicidal compounds for in vivo approach

The most common method for identifying microalga metabolites with herbicidal potential is the in vivo testing method, a method easily adaptable to most laboratories. These tests can fill a large target panel ranging from seed germination inhibition or seedling growth to inhibition of the photosynthetic system and, all with the ability to vary abiotic factors. Two duckweed models, *Lemna minor* and L. *gibba*, have often been used as a model plant to test biological control products with herbicidal effect because of their rapid growth. *Lemna minor* has even been adopted by the U.S. Environmental Protection Agency (EPA) as an aquatic model for conducting phytotoxicity tests (EPA 712-C-96-156). For example, Entzeroth et al. [85] used *Lemna* to identify herbicidal compounds from ethanol extracts of the cyanobacterial species, *Lyngbya aesturii*. Thanks to bioguided fractionation, they were able to demonstrate the presence of 2,5-dimethyldodecanoic acid (Fig. 3). This fatty acid is responsible for inhibiting growth at very low concentrations (200 ng/mL). *Lemna* was also used to assess the phytotoxic activity of usnic acid (Fig. 14), which is not an algal metabolite in the strict sense but a metabolite of lichens (composite organisms composed of a fungus harbouring an algal symbiote) known for its herbicidal activity and also acting on monocotyledonous and dicotyledonous agricultural plants such as corn and sunflower [161]. More recently, several studies [122,162,163] used *Lemna minor* to study the effects of microcystins (Fig. 10) on plant growth. These studies have shown that microcystins can inhibit the growth and photosynthesis of *Lemna*. However, they did not show the inhibitory effects extracts of the cyanobacteria themselves on *Lemna* [122].

Several studies on various model species of aquatic plants such as *Myriophyllum spicatum*, *Ceratophyllum demersum*, *Phragmites australis* [163–165] have been conducted to study the phytotoxicity of microalgal metabolites. Meanwhile, other scientists have been interested in agricultural models in order to extend the phytotoxic potential of algal metabolites as a biocontrol agent. For example, Sanevas et al. [166] evaluated hydro-alcoholic extracts of a cyanobacteria, *Hapalosiphon*, on monocotyledonous and dicotyledonous plant species (radishes, cabbage, etc.). The results highlight a dose-dependent inhibition of root growth but also, an inhibition of the elongation of the shoots due to the inhibition of cell division. Hassan and Ghareib [76] have shown that extracts from a strain of *Nostoc*, isolated from an agricultural pond, specifically inhibit root growth as well as seedling shoots, but the extracts do not affect the germination of rice grains of *Oryza sativa*. Gleason et al. [167] have shown that cyanobacteria extracts of *Scytonema hofmanni* also inhibit the growth of agricultural plant species such as corn and peas. In addition, it has an effect on wild plant species such as *Rumex crispus*, *Polygonium convolvulus* and *Avena fatua*. Several studies [165,168,169] have evaluated the possible impacts of microcystins on different agricultural species such as potatoes, mustard, beans, corn, lentils, peas, wheat and spinach. The results emphasize the fact that microcystin-LR inhibits the length growth of epicotyls and roots and corn kernel germination. Even if microcystin-LR have inhibition activity on plants, the cyanobacteria that produced it had no activity on aquatic plants as seen above with *Lemna minor*.

6.3. Microalgae herbicidal compounds for target-based approach

The abundant literature on the specific and targeted modes of action of molecules with herbicidal properties derived from natural products [170–174] illustrates the high level of community activity in the search for new targeted herbicides. In target-based approach, commercial herbicides generally fall into several categories based on their biochemical, molecular or cellular "mechanisms of action" [175]. Among these, we highlight 4 categories:

1. Inhibition of oxygenated photosynthesis including photosystems I and II (PSI/II) and inhibition of the biosynthesis of associated pigments;

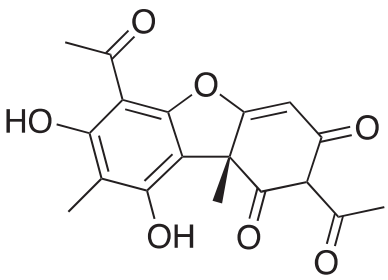

Fig. 14. Usnic acid.

2. Molecular imitation by mimicry of plant growth regulators such as auxines, cytokinins, etc.,
3. Inhibition of microtubules or other components of cell division,
4. Inhibition of the primary metabolism and more specifically the biosynthesis of lipids and "branched" and aromatic amino acids.

6.3.1. Inhibition of oxygenated photosynthesis and biosynthesis of pigments

Gantar et al. [89] highlighted, via the use of pulsed amplitude modulated fluorescence (PAM), that lipophilic extracts of the cyanobacterial strain *Fischerella* 52-1, specifically inhibited photosystem II (PSII) while contributing to the degeneration of thylakoids. This result is particularly remarkable because this strain produces hapalindoles. Similarly, fischerellins (Fig. 6) have been shown to significantly inhibit PSII by acting specifically at several sites completely separate from the target site of diuron (Fig. 15) (3-(3,4-dichlorophenyl)-1,1-dimethylurea), a herbicide known for its PSII inhibition action [176] and which acts mainly in competition with plastoquinone [177]. Through this study, the authors demonstrated that in the short term fischerellins inactivate the reaction centers of the PSII and, in the long term, deconstruct the PSII, thus preventing energy transfer via the reaction center. The cyanobacterium *Scytonema hofmanni* also has the potential to inhibit, with an activity five times greater than diuron, PSII on a site separate from the diuron. Its action targets the oxidation site of the quinone-B electron acceptor [98,167].

6.3.2. Mimicry of plant growth regulators

The mimicry inhibition of plant growth regulators and more specifically hormones such as gibberellins, auxins and cytokinins are studied as herbicides. Although growth regulators are involved in the growth of higher plants (cell division, lengthening), directed application of agonists can lead to uncontrolled growth and, therefore, act as herbicides. Microalgae, especially cyanobacteria and chlorophytes, produce extracellular compounds that act as the three types of hormones mentioned above. Zulpa et al. [159] were able to demonstrate that the culture medium of the cyanobacteria *Nostoc* exhibited an auxin-like dependent activity. They then showed that the extracellular products of *Scytonema hofmanni* stimulated the growth of *Lilium alexandrae* in a similar way to the synthetic auxin, 1-napthaleneacetic acid (NAA). The work of Sergeeva et al. [179] screened 34 strains of cyanobacteria. Among these, 21 strains release auxin-like indolic substances and the presence of indole-3-acetic acid (IAA) (Fig. 7) was confirmed in two species of the genus *Nostoc*. Greater "auxin-like" activity was found for symbiotic species (83%) compared to free species (38%). More recently, Hussain et al. [180] have identified IAA and zeatins (cytokinins) in several strains of cyanobacteria (*Anabaena* sp. Ck1, *Oscillatoria* sp. Ck2, *Phormidium* sp. Ck3, *Chroococcidiopsis* sp. Ck4, and *Synechosystis* sp. Ck5). Cyanobacteria have also been shown to produce extracellular metabolites that act as gibberellin-like plant growth regulators [181].

6.3.3. Cell division inhibitor

Microalgae produce a wide variety of cell division inhibitors and these metabolites have been widely studied for their potential as antibiotics or anticancer drugs. These compounds act as synthetic regulators of plant growth (effects on cell lengthening, swelling, etc.) by affecting cell division through direct mechanisms, such as inhibition of tubulin/microtubule assembly, rather than indirect mechanisms like the regulation of gene expression. In this context, the most studied family of metabolites from microalgae are peptides from the cryptophycin family [182]. Cryptophycins (Fig. 11) are composed of more than 25 metabolites specifically isolated from the genus *Nostoc* and play a direct role in microtubule depolymerisation [183]. Similarly, other cyanobacterial peptides, such as curacin A from *Lyngbya majuscula* and dolastatins from *Symploca* sp. (Fig. 11), are inhibitors of microtubule assembly and tubulin polymerization [184]. A wide range of non-ribosomal peptides have been isolated from cyanobacteria and microalgae, characterized and selected for possible applications in the medical field [77,112].

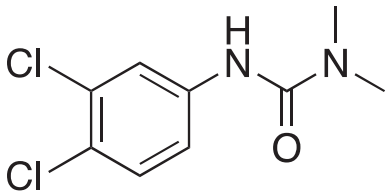

Fig. 15. Diuron.

Despite this focus on cell division inhibitors derived from microalgal extracts for the medical field, studies have also shown that activity on cell division is equivalent in plant tissues. Therefore, the use of these compounds as potential herbicides is also an alternative to the use of synthetic herbicides. Sanevas et al. [166] showed that extracts of the cyanobacteria *Hapalosiphon* inhibit the growth of roots and aerial parts in many agricultural plants and more precisely, extracts inhibit plant mitosis. In another study using the model plant *Arabidopsis thaliana* [185], the authors tested the effect of okadaic acid (Fig. 1) as inhibitors on the protein phosphatase of root cortical microtubules. Although this toxin is known as a protein and serine/threonine phosphatase inhibitor, it has other effects. Okadaic acid affects both cellular lengthening and expansion at higher concentrations. Although the toxicity of this metabolite can obviously limit the potential of the compound itself as commercial herbicide, the differential activity of this metabolite requires further study, especially on its phytotoxic effects.

6.3.4. Inhibitor of the biosynthetic pathways of primary metabolites

A final mechanism, somewhat less studied because of its complexity, is the inhibition of the biosynthetic pathways of primary metabolites (including lipids and amino acids). Among the best known examples are inhibitors of amino acid biosynthesis [186] such as inhibitors of acetolactate synthase or ALS (e.g., sulfonylurea) and 5-enolpyruvylshikimate-3-phosphate synthase (ESPS) (e.g., glyphosate). These inhibitors play a key role in the steps of branched chains and aromatic amino acid synthesis, and the ALS pathway, which only exists in plants, make it a particularly promising target for herbicide research. Similarly, inhibitors of the enzyme acetyl-coA carboxylase (ACCase) act on the inhibition of a key step in lipid biosynthesis, and show selective activity, between monocotyledons and dicotyledons. This is a promising second target for the development of new herbicides.

To date, there is no known metabolite from microalgae that targets amino acid or lipid biosynthesis pathways. However, the great diversity of lipids and amino acids produced by microalgae suggests that microalgae use novel biosynthetic pathways and specific enzymes to form "special" lipids and amino acids not recognized by conventional enzymatic pathways. It is therefore these "special" enzymatic pathways that can potentially be the source of inhibitors of classical lipid/amino acid biosynthesis and should be explored in the search for herbicidal agents. For example, cyanobacteria are known to produce and use a wide range of "special" amino acids such as D isomers, β-hydroxylated and *N*-methylated residues, fatty acid derivatives, etc. [187]. Several studies [188,189] have also demonstrated an apparently widespread tolerance of cyanobacteria to ESPS inhibitors and glyphosate. One study showed the ability of cyanobacteria to inhibit enzymes involved in amino acid catabolism [10]. Norharmane (Fig. 6) is responsible for inhibiting an enzyme equivalent to indoleamine 2,3-dioxygenase which is involved in the catabolism of tryptophan [90]. Another study reported that the toxin synthesized by the lichen, usnic acid (Fig. 14) inhibits the action of hydroxyphenylpyruvate oxygen (HPPD), resulting in the blocking of plastoquinone synthesis and the "bleaching" of plant cells [10]. This mechanism is similar to commercial herbicides in the triketone family. But although the combination of microalgae and lichen fungus provides the necessary context for the production of usnic acid, it can also be assumed that a significant part of this baggage comes mainly from the

symbiotic fungus, since usnic acid derivatives are produced by fungi [190–192].

From a general point of view, studies on these mechanisms of action suggest an open space for research and discovery of new metabolites with herbicidal potential. Their development remains restricted by uncompetitive economic models, mainly due to our dependence on fossil fuels and heavy industry. The low price of non-renewable energy (oil, gas and coal) and the lack of resolutely sustainable policies are delaying the energy, ecological and social transition.

Microalgae consist of multiple lineages over long evolutionary lines giving rise to an extensive and diverse biodiversity of compounds. This underlying chimiodiversity offers the opportunity to develop tomorrow's biocontrol products through original molecules [193]. Technological and scientific advances, in their current dynamics, will lead to the rapid development of industrial microalgal crops in the coming years. This will make it possible to explore this pool with infinite potential for research and discovery of new metabolites with herbicidal potential.

7. Conclusion

Microalgae are a rich source of bioactive metabolites with herbicidal potential. They synthesize many compounds with indirect biological activity such as algicides or direct such as photosynthesis inhibitors, antimitotics. Although a number of micro-algal metabolites have been directly or potentially recognized as having herbicidal or algicidal activity, there is a clear need for further knowledge on these metabolites. In many cases, the compounds studied as herbicides or algicides are known to be potentially toxic to humans or animals, which limits their direct use as herbicides. This is particularly true for several toxins derived from algal blooms (HAB) which, despite the allelopathic and herbicidal effects, have a high toxicity on humans as well as negative impacts on flora and fauna. Although such toxicity is likely to occur with direct commercial application of these compounds, further work would provide a means of identifying possible new targets for the development of less toxic herbicides based on their mechanisms of action. Further identification of metabolites with herbicidal activity, evaluation of specific taxa (e.g., monocotyledons versus dicotyledons), differences in activity, and a deeper understanding of the mechanisms of action, would permit the assessment on the potential use of these compounds. Finally, despite the clear potential of this resource for herbicide discovery and development, commercial exploration remains extremely limited. To our knowledge, only one patent has been submitted (U.S. Patent 4626271) specifically based on the works of Gleason et al., (1986); Gleason and Case, (1986); Gleason and Paulson, (1984) [98,99,167] on the algicide and herbicide activity of cyanobacterin for the explicit use as a green herbicide.

Despite the potential of cyanobacteria strains and of microalgae as biocontrol agents, the use of microalgae or compounds derived from microalgae to ensure higher agricultural yields and a positive transition to agro-ecology, is still in its infancy. New trials are using metabolites of cyanobacteria and microalga to produce commercial products for sustainable agricultural development. However, all the experiments were conducted under laboratory conditions, and very few are carried out in a natural environment. Therefore, research is needed to translate the lab experiment results into field experiments in order to determine the feasibility of application. This step can be extremely difficult. The introduction on the market of new biocidal products is strictly regulated by the European Parliament (example of the regulation n°1107/2009 of the European Council on plant protection products) [194]. In addition, the REACH regulation (Registration, Evaluation, Authorization and restriction of CHemicals), aims to identify, evaluate and control chemical substances manufactured, imported and placed on the European market in order to improve knowledge of the effects of certain products on human health and the environment and to take appropriate measures, particularly legal measures. In France, these regulations are reinforced by the Grenelle de l'environnement and the Ecophyto plan [194]. However, the study of Marchant et al. [195] aims at pointing out the drawbacks of the approval process for biocontrol agents as active substances under the European Public Private Partnerships (PPP) regulation. It shows that some chemical substances have been approved, while other biocontrol agents have not been approved despite having similar toxicological data. More than 30 applications for promising biocontrol agents have not been approved under EU PPP regulations since 2007. These pitfalls seriously harm the development of renewable biocontrol agents. We would strongly advocate for the continued exploration into the chemical diversity of allelochemicals and the pathways leading into greener alternatives.

CRediT authorship contribution statement

Slimane Chaïb: Writing - Original Draft, Review & Editing **Jennifer C.A. Pistevos**: Writing - Review & Editing **Cédric Bertrand**: Supervision, Writing - Review & Editing **Isabelle Bonnard**: Supervision, Writing - Review & Editing.

Declaration of competing interest

No conflicts, informed consent, or human or animal rights are applicable to this study.

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